

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 2003/082211 A3

(51) International Patent Classification⁷: **C12N 1/00**,
A01N 61/00, A61K 31/00

(21) International Application Number:
PCT/US2003/009629

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/368,417 27 March 2002 (27.03.2002) US

(71) Applicant (for all designated States except US): **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 12 Floor, Oakland, CA 94607-5200 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GORDON, Adrienne, S.** [US/US]; 23 Norwood Avenue, Kensington, CA (US). **DIAMOND, Ivan, F.** [US/US]; 761 San Diego Road, Berkeley, CA (US). **YAO, Lina** [—/—]; * (**).

(74) Agents: **QUINE, Jonathan, Alan et al.**; Quine Intellectual Property Law Group, P.C., P.O. Box 458, Alameda, CA 94501 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
16 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYNERGY OF DOPAMINE D2 AND ADENOSINE A2 RECEPTORS ACTIVATES PKA SIGNALING VIA BETA/GAMMA DIMERS

(57) Abstract: This invention pertains to the discovery that a dopamine receptor agonist can activate PKA signaling and/or can act synergistically with an adenosine receptor to activate such signaling. In various embodiments, this invention exploits the synergy between the dopamine receptor pathway and an adenosine receptor pathway to provide methods of mitigating one or more symptoms produced by the chronic consumption of a substance of abuse or to mitigate one or more physiological and/or behavioral symptoms associated with cessation of chronic consumption of a substance of abuse. In certain embodiments, the methods involve administering to the mammal an effective amount of an adenosine receptor antagonist; and an effective amount of a dopamine receptor antagonist; where the effective amount of the adenosine receptor antagonist is lower than the effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist.

WO 2003/082211 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/09629

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 1/00; A01N 61/00; A61K 31/00

US CL : 435/810, 811, 812; 514/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/810, 811, 812; 514/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOUCH, M. et al., Regulation of sensorimotor gating by interactions of dopamine and adenosine in the rat, Behavioural Pharmacology, 1998, Vol 9, No 1, pages 23-29, see the Abstract and Experiment 1 on page 24.	21-35, 58-77, 134-149
A	MAILLIARD-W.S. et al., Recent advances in the neurobiology of alcoholism: the role of adenosine, Pharmacology & Therapeutics, 2004, Vol 101, pages 39-46, see the entire article.	1-149
A	WALTER, H. et al., Dopamine and Alcohol Relapse: D1 and D2 Antagonists Increase Relapse Rates in Animal Studies and Clinical Trials, Journal of Biomedical Science, 2001, Vol 8, pages 83-88, see the entire article.	1-149

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

07 October 2004 (07.10.2004)

Date of mailing of the international search report

04 NOV 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Michael Bannock

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

PCT/US03/09629

Continuation of B. FIELDS SEARCHED Item 3:

STN: MEDLINE, BIOSIS; West 2.1

search terms: Dopamine, D1, D2, adenosine, A1, A2A, agonist, antagonist, synergy, cooperativity, PKC, PKA, beta-gamma, translocation, accumbens, striatal, VTA, reinforcing, addiction, abuse, ethanol, opiate, cannabinoid, NG108-15